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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
SHAFER, SHULAMITH H	

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1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/630,227	DIMAURO ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2010 and 08 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-43,45-48,50-58,60-79,84-88 and 91-96* is/are pending in the application.

4a) Of the above claim(s) *3-13,35,52,66-79 and 84-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,34,36-43,45-48,50,51,53-58,60-65,91-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/8/2010,2/8/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application in response to the Notice of Defective Appeal Brief mailed of 6 July 2009. In lieu of filing an amended appeal brief, a filing of request for continued examination and an amendment in response to the Office Action of 27 June 2006 have been presented. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, Applicant's submission filed on 6 January 2010 has been entered.

Applicants' response of 6 January 2010 has been entered. A paragraph on page 15, lines 11-29 of the instant specification has been amended to correct typographical errors and update trademark status.

Claims 49, 80-83 and 89-90 have been canceled. Claims 1, 46, 50, 91 and 92 have been amended and the amendment made of record. Claims 93-96 are newly presented and entered into the record.

In response of 4 February 2011, to requirement for election/restriction, applicants elect, with traverse, BMP-7 and infliximab as the species for prosecution. The reasons for the traversal are:

The search and examination regarding the previously elected species "growth factors" were already performed and the Examiner has issued several subsequent Office Actions on the merits. In fact, a claim directed specifically to a growth factor which is a "bone morphogenetic protein" was previously presented on April 4, 2006 as Claim 91, and the Examiner has examined that claim. Because the species set forth in the current Species Election # 1 are fully embraced by the previously elected species of "growth factor" and because a claim directed specifically to "bone morphogenetic proteins" has been previously examined, the burden on the Examiner for examining claims directed to the individual "growth factors" would not be a serious one.

For Species Election #2, the Examiner requires election of one antibody directed against TNF-alpha from a list of three monoclonal antibodies: adalimumab, CDP-571 and CDP-870. The search and examination regarding the previously elected species "inhibitors of TNF-a synthesis" were already performed and the Examiner has issued several Office Actions on the merits. In fact, a claim directed specifically to an inhibitor of TNF-alpha synthesis which is a "monoclonal antibody" was previously presented on April 4, 2006 as Claim 89. Because the species set forth in the current Species Election #2 are fully embraced by the previously elected species of "inhibitors of TNF-alpha synthesis" and because a claim directed specifically to a "monoclonal antibody" has been previously examined, the burden on the Examiner for examining claims directed to the individual "anti-TNF-alpha monoclonal antibodies" shown in Claims 93-95 should be, at most, minor and not serious.

Applicants' arguments have been deemed persuasive. The requirement for species election is hereby withdrawn.

Claims 1-13, 15-43, 45-48, 50-58, 60-79, 84-88 and 91-96 are pending in the instant invention. Claims 3-13, 15-33, 35, 52, 66-79 and 84-88 stand withdrawn as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 2, 34, 36-43, 45-48, 50, 51, 53-58, 60-65 and 91-96 are under consideration.

Withdrawn Rejections

Claims 49, 80-83, 89 and 90 have been canceled; all rejections and objections of these claims are therefore moot.

The rejection of claims 38 and 48 under 35 U.S.C. 112, second paragraph, is withdrawn, as previously noted in response to Applicants' Appeal Brief, and in light of Applicants' amendment to Claim 1 to recite a specific agent, an anti-TNF-alpha monoclonal antibody.

The rejection of claims 38 and 48 under 35 U.S.C. 112, first paragraph (enablement), is withdrawn, as previously noted in response to Applicants' Appeal Brief, and in light of Applicants' amendment to Claim 1 to recite a specific agent, an anti-TNF-alpha monoclonal antibody.

The rejection of claims 46, 49, 91 and 92 under 35 U.S.C. 112, first paragraph (enablement), is withdrawn in light of Applicants' amendment to Claim 1 to recite a specific agent, an anti-TNF-alpha monoclonal antibody.

The rejection of claims 49, 91 and 92 under 35 U.S.C. 112, first paragraph (written description), is withdrawn in light of Applicants' amendments to the Claims.

Applicants' amendment to the claims are sufficient to overcome the following rejections over the prior art:

The rejection of claims 1, 2, 34, 37, 47, 51, 54 and 56 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Dunn (2001, EP 1 153 607)

The rejection of Claims 36, 39-43, 45, 58, 60-65 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al in view of Pike et al. (2003, US PG PUB 2003/0134792)

The rejection of Claim 50 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al, and Dunn as applied to Claim 1 and Molloy et al. (2003, Sports Med 33:381-394)

The rejection of Claims 1, 53 and 57 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al in view of Smith et al. (2002, PG PUB US 2002/0169162)

The rejection of Claim 55 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al and Dunn as applied to Claim 1 in view of Cardone et al (2003, American Family Physician, 67:2147-2152)

The rejection of Claim 91 and 92 under 35 U.S.C. 103 (a) as being unpatentable over Lehman and Dunn as applied to claim 1 in view of Wolfraim et al. (2004, U.S. 6,756,215, filed 19 October 2001)

New Grounds of Rejection

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 34, 36-43, 45-48, 50, 51, 53-58, 60-65 and 91-96 are rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, one of the independent claims of the instant invention has been amended to recite “a formulation comprising an effective amount of an inhibitor of TNF-alpha synthesis, wherein the inhibitor of TNF-alpha synthesis is an anti-TNF-alpha monoclonal antibody or antigen-binding fragment thereof”. Claim 96, the other independent claim is drawn to administration of “an effective amount of an inhibitor of TNF-alpha synthesis, wherein the inhibitor of TNF-alpha synthesis is infliximab”.

The art, at the time the instant invention was made, (see, for example, Brekke et al. Nature Reviews, Drug Discovery 2003. 2:52-62) teaches that therapeutic antibodies, such as ones recited in the claims of the instant invention, act by blocking the action of specific molecules. The blocking activity of therapeutic antibodies is achieved by preventing growth factors, CYTOKINES or other soluble mediators reaching their target receptors, which can be accomplished either by the antibody binding to the factor itself or to its receptor (page 52, 2nd column). Specifically, with respect to antibodies directed against TNF-α, such as infliximab (Remicade), CDP-571, CDP-870 and adalimumab (as recited in claims 96, 94, 95 and 93, respectively), the reference teaches that such antibodies bind to the specific cytokine, in this case TNF-α (page 55, 1st column, last

paragraph, bridging page 56, 1st column). Information submitted by the Applicants (6 January 2010, Exhibit D) teach that infliximab (Remicade) is a monoclonal antibody that binds specifically to human tumor necrosis factor alpha (page 1, 1st paragraph) and inhibits binding of TNF-alpha to its receptors (page 2, 1st paragraph). Thus, it is unclear how the anti-TNF-α antibody, which specifically binds to TNF-α, thereby preventing the cytokine binding to its cognate receptor, would be able to inhibit synthesis of the cytokine.

The remainder of the claims is included in the rejection as dependent upon a rejected claim.

Claim Interpretation

The claims are drawn to a method of treating an inflamed orthopedic joint, said method comprising trans-capsularly administering into the joint space a formulation comprising trans-capsularly administering into the joint space a formulation comprising an effective amount of an inhibitor of TNF-α synthesis, wherein the inhibitor of TNF-α synthesis is an anti-TNF-α monoclonal antibody or antigen-binding fragment thereof. It is the Examiner's position that art teaching administration of an anti-TNF-α monoclonal antibody to treat an inflamed orthopedic joint meets the limitations of the claims. The art is not required to propose a mechanism of action for said anti-TNF-α monoclonal antibody. Claims 38, 46, 48, 51, 55, 63, 65 and 93-95 all recite "inhibitor of TNF-α synthesis"; these claims all depend from Claim 1, which identifies the inhibitor of TNF-α synthesis as an anti-TNF-α monoclonal antibody. It is the Examiner's position that a formulation comprising an anti-TNF-α monoclonal antibody meets the limitations of the claims.

35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 34, 36-38, 47, 48, 51, 54, 56, 58 and 91 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Fischkoff et al (US 2003/0235585, filed 5 June 2002) in view of Dunn (2001, EP 1 153 607).

The cited references provide the following teachings:

Fischkoff et al. teaches a method for treating disorders in which TNF-alpha activity is detrimental. The methods include administering subcutaneous injections of antibodies to a subject. The antibodies preferably are recombinant human antibodies that specifically bind to human TNF-alpha. These methods include utilizing a combination therapy wherein human antibodies are administered to a subject with another therapeutic agent [paragraph 0009]. One of the diseases and conditions to be treated by the disclosed methods is joint destruction in rheumatoid arthritis (RA) [paragraph 0111]; among the joints affected by RA are knee joints (as evidenced by Rheumatoid Arthritis, MedicineNet.com

http://www.medicinenet.com/script/main/art.asp?articlekey=466&pf=3&page=1, downloaded 4/22/2011, page 4, 2nd paragraph). Thus, the reference teaches administration of recombinant human antibodies that specifically bind to human TNF-alpha to treat an inflamed orthopedic joint wherein the joint is a knee joint. The reference also teaches that local administration of the antibody or antibody portion at a site of inflammation may be beneficial (e.g., local administration in the joints in rheumatoid arthritis) [paragraph 0112]. Fischkoff et al. teach that the most preferred recombinant antibody of the invention, is D2E7, also known as adalimumab, a fully human anti TNF-α monoclonal antibody (as evidenced by Weinblatt et al. 2003. Arthritis and Rheumatism 48:35-45, title). The reference teaches that the composition comprising the required antibodies may be administered as liposomes [paragraph 0086]; various doses are also disclosed, an "effective amount of an antibody or antibody portion of the invention is 10-100 mg" [paragraph 0098].

Fischkoff et al also teach "A therapeutically effective amount of the antibody or antibody portion may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual" [paragraph 0096]. "Dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic or prophylactic response)…. [paragraph 0097].

Fischkoff et al does not specifically teach transcapsular administration of the formulation into the knee joint, the transcapsular administration of a formulation comprising at least one growth factor, wherein the formulation is administered in an amount of less than 1 cc, the administration of the formulation closely adjacent to the outer wall of the capsule, wherein the inhibitor of TNF-α sythesis therapeutically inhibits the production of a cytokine, the administration of a formulation that includes a viscosupplement and the administration performed through a needle.

Dunn (EP 1 153 607) teaches the injection of a mixture of purified growth hormone and buffer solution into the joint (abstract, page 1), to treat inflammation of a joint, and specifically discloses treatment of a knee joint (column 1, 0001, line 5-7). The reference teaches the injection of a group of agents such as anti-cytokines (column 3,

0008, lines 45-47), which would by definition include an inhibitor of TNF-α synthesis and anti-TNF-α mono-clonal antibodies. Dunn discloses that the method may include an additional step of mixing Lidocaine (an additional therapeutic agent) with the mixture of (Column 4, 0012, lines 11-14), that a preferred volume is generally between 0.5 to 10 milliliters (column 8, 0029, lines 39-40) and that the formulation is injected utilizing a syringe into the joint space and not directly into the bone or tissue (column 7, 0027, lines 30-32, and figure 2). The reference teaches that the invention may additionally comprise the use of a lubricant or viscosupplement such as purified hyaluronic acid or hyaluronate salt (column 9, 0032, lines 25-28). Viscosupplementation is defined as a "procedure that involves the injection of gel-like substances (hyaluronates) into a joint to supplement viscous properties of a synovial fluid" (http://arthritis.about.com/od/kneetreatments/g/viscosupplement, downloaded 12/9/05). Dunn teaches the administration of a therapeutic agent as a means of regenerating articular cartilage in the joint, thus achieving repair of joint tissue.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the administration route taught by Fischkoff et al which teaches the advantages administration of anti-TNF-α monoclonal antibodies at a site of inflammation and use the administration route taught by Dunn, the injection of a therapeutic formulation into the joint. The person of ordinary skill in the art would have been motivated to make that modification because Fischkoff et al teaches the advantages of administration of the therapeutic formulation at the site of inflammation and discloses the administration of combination therapy wherein human antibodies are administered to a subject with another therapeutic agent and Dunn discloses a preliminary step involving treatment of the joint with "a group of agents such as anti-cytokines, …..so as to reduce or remove deleterious activity in the joint" (column 3, 0009, lines 38-44). The skilled artisan reasonably would have expected success because both Fischkoff et al. and Dunn discloses the injection of therapeutic agents into the joint to treat joint inflammation.

With regard to the specific dosages and concentrations recited in claims 38, 48, and 58: One of ordinary skill in the art at the time of the instant invention would have

reasonably known that dosage amounts are results-effective variables that are routinely optimized in the art. There is no evidence in the prior art that Applicant's claimed ranges are critical to the functionality of the claimed invention. Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In reAller, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955). Based on the teachings of Fischkoff et al. and Dunn, the concentration ranges of anti-TNF-α monoclonal antibodies are nothing more than ranges which can be achieved through routine experimentation that can be optimized on an individual basis, depending on the intended use and route of administration (see In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977; and In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980)).

One of ordinary skill in the art would be motivated to combine the references because they are drawn to the same field of endeavor, treatment of inflamed orthopedic joints, and the cited prior art references provide motivation for solving the problem of reducing inflammation when administered to an inflamed orthopedic joint.

Claims 39-43, 45, 46, 60, 61-65 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Fischkoff et al in view of Dunn (2001, EP 1 153 607) as applied to Claim 1 further in view of Pike et al. (2003, US PG PUB 2003/0134792).

The teachings of Fischkoff et al and Dunn are disclosed in detail above. The references, singularly or in combination do not disclose a formulation further comprising a sustained, controlled release device, providing continuous release, or intermittent release, a hydrogel, a formulation in a patch attached to an outer wall of the capsule, a formulation in a depot closely adjacent an outer wall of the capsule, the release of the antagonist by diffusion through a sustained delivery device, a polymer sustained delivery device, microspheres having a plurality of degradation rates or wherein the antagonist is released by biodegradation of a sustained delivery device.

Pike et al disclose a method for treating articular cartilage disorders, such as disorders of the knee [paragraph 0059] by administration of therapeutic agents that preserve existing cartilage tissues or stimulate regeneration of cartilage [paragraph 0002]. Pike et al teach administration of a therapeutically effective dose directly at the site with a sustained release device [paragraph 0053 and claim 7], which would, by definition, comprise a controlled release device providing continuous release. The reference teaches that the device may be implanted within the diseased or injured joint [paragraph 0053], which would encompass attachment to the outer wall of the capsule, or a depot closely adjacent to an outer wall of the capsule or a location closely adjacent to an endplate of an adjacent bony body. Pike et al teach the formulation may be enclosed in a semipermeable matrix of hydrophobic polymers [paragraph 0044], which would allow for diffusion for the high specificity antagonist through a sustained delivery system [paragraph 0044]. The reference teaches the use of hydrogels and microcapsules [paragraph 0044] made of different materials, which would inherently have a plurality of degradation rates and comprise a device which provides intermittent release [paragraph 0044 and Claim 5]; the reference also discloses the release of a therapeutically effective level of an agent as the matrix degrades [paragraph 0053].

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the administration of the formulation comprising an anti-TNF-alpha monoclonal antibody, as taught by Fischkoff et al. and Dunn and utilize the delivery systems disclosed by Pike et al. The person of ordinary skill in the art would have been motivated to make that modification and anticipate success because Fischkoff et al. and Dunn disclose administration of therapeutic formulations at the site of inflammation and Pike et al teach alternative methods of administration of therapeutic agents at the site of inflammation, said methods comprising utilization of a sustained release device, a controlled release device providing continuous release a device implanted within the diseased or injured joint, a semipermeable matrix of hydrophobic polymers, hydrogels or microcapsules made of different materials

Claim 50 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Fischkoff et al in view of Dunn as applied to Claim 1 further in view of Molloy et al. (2003, Sports Med 33:381-394). The teachings of Fischkoff et al and Dunn are disclosed in detail above.

The references, singularly or in combination, do not teach the specific use of a formulation comprising growth factor derived from platelet concentrate.

Molloy et al teach that PDGF plays a significant role in early stages of healing (page 387, Column 1, Section 1.4, paragraph 1). The reference teaches that the introduction of PDGF into the injury site of healing rabbit femur-MCL-tibia complexes increases the quality of healing (page 390, column 1, paragraph 2 and Table III).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating an inflamed orthopedic joint as taught by Fischkoff and Dunn, said method comprising administration of anti-TNF-α monoclonal antibodies and additional therapeutic agents, including growth factors into the joint space and add a growth factor such as PDGF as taught by Molloy et al. The person of ordinary skill in the art would have been motivated to make that modification and anticipate success because both Fischkoff and Dunn teach the administration of additional therapeutic agents and Molloy teach that PDGF has vital functions during early and intermediate stages of healing (page 391, column 2, 2nd paragraph).

Claims 53 and 57 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Fischkoff et al in view of Dunn as applied to Claim 1 further in view of Smith et al. (2002, PG PUB US 2002/0169162).

The teachings of Fischkoff et al and Dunn are disclosed in detail above.

The references, singularly or in combination, do not disclose the injection of the formulation into the synovial fluid or the administration of the formulation through a drug pump. Smith et al teach an implantable sustained release device for locally administering a therapeutically effective compound to a joint (paragraph 0017),

including a knee joint (paragraph 0070). The device is a mechanical one implanted intraarticularly to deliver a therapeutically effective compound within a synovial capsule of the joint (abstract). The reference teaches administration of a therapeutically effective compound to the synovial fluid of a joint (paragraph 0041).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating an inflamed orthopedic joint as taught by Fischkoff and Dunn, said method comprising administration of anti-TNF-α monoclonal antibodies into the joint space and administer said formulation using the pump device disclosed by Smith et al. The person of ordinary skill in the art would have been motivated to make that modification anticipate success because the art Fischkoff and Dunn teach administration of therapeutic formulations directly to the site of inflammation and Smith et al teach an alternative administrative device that could be used to release drugs over an extended period of time in a controlled fashion to treat a knee joint.

Claim 55 is rejected under 35 U.S.C. 103 (a) as being unpatentable over over Fischkoff et al in view of Dunn as applied to Claim 1 further in view of Cardone et al (2003, American Family Physician, 67:2147-2152).

The teachings of Fischkoff et al and Dunn are disclosed in detail above.

The references, singularly or in combination, do not disclose removing a portion of synovial fluid prior to administration of the antagonist. Cardone et al teach a method of removing fluid from the knee joint by aspiration (page 2147, abstract, page 2151, column 2, paragraph 2).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating an inflamed orthopedic joint as taught by Fischkoff and Dunn, and aspirate fluid from the knee joint prior to administration of the therapeutic formulation, as suggested by Cardone et al. The person of ordinary skill in the art would have been motivated to make that modification

and anticipate success because Cardone et al teach that aspiration may be performed to aid in diagnosis and relieve discomfort and teaches detailed technique for performing this procedure (entire paper).

Claims 91 and 92 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Fischkoff et al in view of Dunn as applied to claim 1 further in view of Boyle (US 7,097,834, filed 14 December 1998).

The teachings of Fischkoff et al and Dunn are disclosed in detail above. The references, singularly or in combination, do not teach a method wherein the formulation further comprises BMP-1, BMP-3, BMP-2, OP-1, BMP-2A, BMP-2B or BMP-7 or wherein the formulation further comprises TGF-β.

Boyle teaches a method of treatment of bone disorders collectively referred to as osteopenias which include rheumatoid arthritis. Said method comprises administration of compositions comprising bone morphogenic factors BMP-1 to BMP-12 and TGF-β (column 11, lines 50-62).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating an inflamed orthopedic joint as taught by Fischkoff and Dunn comprising administration of a formulation comprising anti-TNF-α monoclonal antibodies and include bone morphogenic factors BMP-1 to BMP-12 and/or TGF-β in said formulation as taught by Boyle.

One of ordinary skill would be motivated to combine the references because they are drawn to the same field of endeavor, treatment of an inflamed orthopedic joint, and the cited prior art references provide motivation for solving the problem of reducing inflammation when administered to an inflamed orthopedic joint. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been

individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 94-96 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Fischkoff et al in view of Dunn as applied to claim 1 further in view of Brekke et al (2003. Nature Reviews, Drug Discovery. 2:52-62).

The teachings of Fischkoff et al and Dunn are disclosed in detail above. The references, singularly or in combination, do not teach a method wherein the inhibitor of TNF-α synthesis is CDP-571, CDP-870 or infliximab.

Bekke et al. teach the development of therapeutic antibodies with high specificity and affinity that bind specific cytokines to inhibit the detrimental effect of the cytokine. Cytokines associated with inflammation and autoimmunity include tumour-necrosis factor-α (TNF-α). Antibodies to TNF-α may be used to treat RA. Marketed products directed towards the regulation of TNF-α include the antibody infliximab (Remicade; Centocor Inc). There are a number of anti-TNF-α antibodies in clinical trials, including CDP571 and CDP870 (Celltech Plc) and adalimumab (D2E7; Abbot Laboratories/Cambridge Antibody Technology) (page 55, 1st column, last paragraph, bridging page 56, 1st column). Thus, the reference teaches that adalimumab, infliximab, CDP-571 and CDP-870, all anti-TNF-α monoclonal antibodies are art-accepted alternatives which may be used to treat rheumatoid arthritis.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating an inflamed orthopedic joint as taught by Fischkoff and Dunn comprising administration of a formulation comprising an anti-TNF-α monoclonal antibody, wherein said antibody is adalimumab and substitute one of the following anti-TNF-α monoclonal antibodies: CDP-571, CDP-870 or infliximab. The person of ordinary skill would be motivated to make such a modification and anticipate success because Bekke teach that all of the listed antibodies bind to TNF-α and may be used to treat RA.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/SHULAMITH H. SHAFER/
Primary Examiner, Art Unit 1647